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Preparation, statistical optimization, and *in vitro* characterization of insulin nanoparticles

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Background and Aims: The aim of this study was preparation, optimization, and in vitro characterization of insulin nanoparticles composed of thiolated diethyl methyl chitosan and thiolated dimethyl ethyl chitosan. These thiolated polymers were synthesized via amide bond between the residual primary amino groups on chitosan backbone and carboxylic group on cysteine.
Methods: Insulin nanoparticles were prepared by the polyelectrolyte complexation method. Experimental design D-optimal response surface methodology was used for the optimization of the nanoparticles. Independent variables were pH of polymer solution, concentration ratio of polymer/insulin and polymer type. Dependent variables include size, zeta potential, polydispersity index (PdI), and entrapment efficiency (EE%). Optimized nanoparticles were studied morphologically by transmission electron microscopy (TEM), and in vitro release of insulin from nanoparticles were determined under phosphate buffer (pH=6.8) condition.
Results: Although a quadratic model has been chosen to fit the responses for size, PdI, and EE%, the zeta potential of the particles has been best fitted to 2-FI model. The optimized nanoparticles were characterized. The size of the particles were found to be 157 and 185 nm; zeta potential were 20.1 and 24.6 mV; PdI of particles were 0.186 and 0.193; and calculated EE% were 87.33% and 70.23% for thiolated diethyl methyl chitosan and thiolated dimethyl ethyl chitosan nanoparticles respectively. TEM images show separated and non-aggregated nanoparticles with sub-spherical shapes and smooth surfaces. An in vitro release study of the prepared nanoparticles showed that the cumulative percentage of insulin released from the nanoparticles were 49.7% and 65.8% for thiolated diethyl methyl chitosan and thiolated dimethyl ethyl chitosan, respectively, within 300 min.

Keywords: D-optimal response surface experimental design methodology; Insulin nanoparticles; Thiolated diethyl methyl chitosan; Thiolated dimethyl ethyl chitosan